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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/822,873	04/02/2001	Peter Kaastrup	KAASTRUP=1A	7206

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EXAMINER	
KIM, YUNSOO	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 12/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/822,873	KAASTRUP, PETER	
	Examiner	Art Unit	
	Yunsoo Kim	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53 and 56-58* is/are pending in the application.

4a) Of the above claim(s) *6-20,52,57 and 58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,21-51,53 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *7/2/2001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Yunsoo Kim, Art Unit 1644, Technology 1600.

2. Applicant's amendments filed on 7/11/2001, 11/08/2001 and 10/07/2002 have been entered.

Claims 1-53 and 56-58 are pending.

3. Applicant's election with traverse of Group I, Claims 1-53 and 56, drawn to an immunogenic composition, the elected species of SEQ ID No:1 and carrier is acknowledged.

The restriction is traversed on the basis of MPEP 821.04, the product claims of Group I being allowable, and the method of use claims being dependent thereon. However, applicant is deemed to request a rejoinder under the product and method claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provision of MPEP § 821.04.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 6-20, 52 and 57-58 are withdrawn from further consideration by the examiner 37CFR 1.142(b) as being drawn to a nonelected invention.

Claims 1-5, 21-51, 53 and 56 drawn to an immunogenic composition comprising a fragment of TGF-beta, wherein the fragment is SEQ ID NO:1, and its functional equivalent obtained by adding at least an amino acid to read on a full length TGF-beta, an immunogenic determinant and a carrier are under consideration in the instant application.

4. Sequence compliance: The instant application appears to be in sequence compliance for patent applications containing amino acid sequence disclosures.

5. Applicant's claim for domestic priority under 35. U.S.C. 119(e) is acknowledged.

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Denmark PA2000 00540 on 3/31/2000. It is noted, however, that applicant has not filed a certified copy of the foreign priority document as required by 35 U.S.C. 119(b). The transmittal filed on 4/2/2001 had indicated provision of the certified copy of the priority document.

6. Applicant's IDS filed on 7/2/2001 is acknowledged. The prior art reference list provided by applicant has been treated as PTO-1449.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-5, 21-51, 53 and 56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an immunogenic composition comprising of a TGF-beta fragment consisting of SEQ ID NO:1, does not reasonably provide enablement for an immunologic composition comprising "fragment" of TGF-beta as recited in claims 1 and dependent claims thereof and 56; or TGF-beta fragment "comprise" the SEQ ID NO:1 as recited in claim 2; or TGF-beta fragment comprises SEQ ID NO:1 including "functional equivalent" thereof obtained by addition, substitution, or deletion of at least one amino acid, of TGF-beta fragment as recited in claims 2-4; or TGF-beta fragment "essentially consists of" SEQ ID NO:1 including functional equivalent thereof obtained by addition, substitution, or deletion of at least amino acid, as recited in claims 3 and 5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use of the invention commensurate in scope with these claims.

The specification disclosure does not enable one skilled in the art to practice the invention without any undue amount of experimentation.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404

(Fed.Cir.1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of the skilled in the art to practice the claimed invention.

The phrase "fragment of TGF-beta" in claims 1 and dependent claims thereof and 56 has not provided sufficient biochemical information that distinctly identifies an immunogenic composition comprising of TGF-beta fragment other than the immunogenic composition comprising of TGF-beta fragment consisting of SEQ ID NO:1. While any TGF-beta fragment contains a highly conserved amino acid sequence of SEQ ID NO:1, the specification fails to provide sufficient guidance and direction as to how the skilled artisan can make such compositions, commensurate in scope with the claimed invention. The specification fails to provide any guidance on how to make and use the immunogenic composition comprising any TGF-beta fragment.

The term "comprise" in claim 2 is open-ended. It expands the amino acid sequence of SEQ ID NO:1 to include additional non-disclosed amino acids. The specification does not provide sufficient guidance as to which amino acid sequence within the polypeptide can be unique and retain a distinct functional capability of TGF-beta fragment.

The phrase "essentially consisting of" in claims 3 and 5 is open-ended. The specification fails to provide sufficient information as to which amino acids to be included without causing deleterious effect to the claimed fragment.

The phrase "functional equivalent" in claims 2-4 renders the TGF-beta fragment to include any TGF-beta fragment obtained by addition, substitution or deletion of at least one amino acid of SEQ ID NO:1. However, the specification fails to provide the sufficient information as to which mutations to be made without causing deleterious effect to the claimed fragment.

Minor structural differences among structurally related compounds or compositions can result in substantially different or deleterious biological activities. As is evidenced in the instant application, various additions, substitutions or deletions and the like provide a range of activities, not all which are necessarily predictive of immunostimulatory TGF-beta as applicant acknowledges that TGF-beta

fragments can be immunosuppressant (e.g. see pages 7-8 overlapping paragraph of the instant specification).

U. S. Pat. No.5,061,786 teaches polypeptides derived from TGF-beta fragment various in lengths from 10 amino acids to 16 amino acids and substitutions at specific sites within the polypeptides are immunosuppressive (see cols 3-5, in particular). Therefore, the functional equivalents comprising any TGF-beta fragment would be expected to have greater differences in their activities.

Ngo *et al* teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495 in particular).

In re Fisher, 166 USPQ 18 indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Since the amino acid sequence of a polypeptide determined its structural property, predictability of which amino acid fragment can retain the functional capabilities of the TGF-beta comprising polypeptide requires knowledge of, and guidance with regard to, which segments in the polypeptide's sequence contribute to its function.

Therefore, there is insufficient direction as to how to make and to use an immunogenic composition comprising any TGF-beta fragment comprising of SEQ ID NO:1 and its functional equivalent molecules which can be used as to whether such a desired effect can be achieved or predicted, as encompassed by the claims.

In view of the quantity of experimentation necessary, the limited working example, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

Applicant is invited to limit the claimed fragment to consisting of SEQ ID NO: 1.

8. Claims 1-5, 21-51, 53 and 56 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of an immunogenic composition comprising of TGF-beta fragment consisting of SEQ ID NO:1; however, applicant is not in possession of an immunologic composition comprising "fragment" of TGF-beta as recited in claims 1 and dependent claims thereof and 56; or TGF-beta fragment "comprise" the SEQ ID NO:1 as recited in claim 2; or TGF-beta fragment comprises SEQ ID NO:1 including "functional equivalent" thereof obtained by addition, substitution, or deletion of at least one amino acid, of TGF-beta fragment as recited in claims 2-4; or TGF-beta fragment "essentially consists of" SEQ ID NO:1 including functional equivalent thereof obtained by addition, substitution, or deletion of at least amino acid, as recited in claims 3 and 5. Consequently, conception in either case cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Revised Interim Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 2-5, 22, and 25-26 are rejected under 35 U.S.C. 112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

(A) The phrase "functional equivalents" recited in claims 2-4 has no antecedent basis in the base claim 1. Only " fragment of TGF-beta" is recited in base claim 1.

(B) The phrase "essentially consists of " in claims 3 and 5 is indefinite for using improper transitional phrase, given that "essentially consists of" is not a standard transitional phrase (see MPEP 2111.03).

(C) The phrase "cytotoxic response" in claim 22 renders the claim indefinite because the nature or the specificity of the cytotoxic response is ambiguous and ill-defined.
It is suggested that applicant amend claim to cytotoxic T-cell response to overcome this rejection.

(D) Claims 25 and 26 have no antecedent basis in base claim 21. Claims 25 and 26 are drawn to T-cells, cytotoxic T-cells, respectively, wherein base claim 21 is drawn to antibody response.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Given that "essentially consists of" is not a standard transitional phrase (see MPEP 2111.03), for examining purpose, the term "essentially consists of" is interpreted to mean the same as "comprising".

Given that claim 2 recites functional equivalent including comprising at least one amino acid addition, the claimed TGF-beta is interpreted to encompass intact TGF-beta for examining purposes.

13. Claims 2-4 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Pat. No. 5,961,979 (IDS reference 24) and in further evidence of Schiott et al. (Scand. J. Immunol. 48, 371-378, 1998, IDS reference 50).

The '979 patent teaches an immunogenic composition comprising an immunogenic determinant and TGF-beta capable of eliciting an immunostimulating effect (see Summary of the Invention including col 7, lines 7-29; Formulation of Vaccine including cols 22-24; Claims 1-7, cols. 26-27 in particular). Schiott et al. is cited as an evidentiary reference. Schiott et al. (Scand. J. Immunol. 48, 371-378, 1998) showed the amino acid sequence of TGF-beta is highly conserved among TGF families (see p. 371, Introduction, in particular). Therefore, the TGF-beta taught by the '979 patent inherently comprises the claimed SEQ ID NO:1.

The '979 reference teachings anticipate the claimed invention, because the functional equivalent obtained by addition of at least one amino acid reads on the TGF-beta taught by the '979 patent.

14. Claims 1-5, 21- 51, 53, and 56 are rejected under 35 U.S.C. 102(b) as being anticipated U.S. Pat. No. 5,874,085 (IDS reference 20) and in further evidence of Schiott et al. (Scand. J. Immunol. 48, 371-378, 1998, IDS reference 50).

The '085 patent teaches a vaccine adjuvant comprising an antigen and TGF-beta (see Summary of the Invention including cols 3-4, in particular). The vaccine adjuvant comprises a carrier and additional adjuvant (see Use of the Claimed Composition including col 11, in particular). The composition is capable of eliciting immunostimulating effects, as well as increase in class of immunoglobulins, (see Description of Preferred Embodiments; col 6, lines 14-44, in particular), and enhances antibody response (see Description of Preferred Embodiments; col 8, lines 6-25, in particular).

In further evidence of Schiott et al. (Scand. J. Immunol. 48, 371-378, 1998), it was known the amino acid sequence of TGF-beta is highly conserved among TGF families (p. 371, Introduction, in particular). Given that TGF-beta comprises SEQ ID NO:1 and Schiott et al. teach the amino acid sequence of TGF-beta is highly conserved, the prior art teaching of TGF-beta anticipates the claimed TGF-beta which comprises SEQ ID NO:1. Thus, it meets the limitations found in the instant claims.
The '085 patent also teaches various combinations of either conjugated fragment, or non-conjugated fragment, either conjugated immunogenic determinant or non-conjugated immunogenic determinant and either conjugated or non-conjugated carrier including combinations of a) conjugated fragment and non-conjugated immunogenic determinant, b) non-conjugated fragment and conjugated immunogenic determinant, c) fragment and immunogenic determinant are conjugated, d) fragment is conjugated to

immunogenic determinant, e) non-conjugated fragment and immunogenic determinant comprising a carrier, f) non-conjugated fragment and immunogenic determinant comprising a non-conjugated carrier, g) non-conjugated fragment and immunogenic determinant comprising a conjugated carrier, h) conjugated fragment and non-conjugated immunogenic determinant comprising a carrier, i) conjugated fragment and non-conjugated immunogenic determinant comprising a non-conjugated carrier, j) conjugated fragment and non-conjugated immunogenic determinant comprising a conjugated carrier, k) conjugated fragment to carrier, l) non-conjugated fragment and conjugated immunogenic determinant comprising a either conjugated or non-conjugated carrier, m) conjugated fragment to immunogenic determinant comprising either a conjugated or non-conjugated carrier, as recited in claims 28-51 (see Use of the Claimed invention; from col 10, lines 60 to col 11, lines 39, and col 2, Table II in particular).

The '085 patent further teaches the use of TGF-beta fragments which retain the TGF-beta activity as intact TGF-beta (see Use of the Claimed Invention, col 19, lines 60-67, in particular). As the TGF-beta fragments retain the TGF-beta activity as intact TGF-beta, TGF-beta fragments are capable of eliciting the immunostimulating effects. The claimed functional limitations recited in claims 21-27 such as cytotoxic T-cell response, and increase level of T-cells and cytotoxic T-cells would be inherent properties of the immunogenic composition comprising TGF-beta and a vaccine.

The reference teachings thus anticipate the instant claimed invention (see entire document including Use of the Claimed Invention and Examples).

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. Claims 1-5, 21-51, 53 and 56 are rejected under 35 U.S.C. 103 as being unpatentable over U.S. Pat. No. 5,874,085 as is evidenced by Schiott et al. (Scand. J. Immunol. 48, 371-378, 1998), in view of U.S. Pat. No. 6,057,430.

The '085 patent and Schiott et al. references have been discussed, supra.

The claimed invention differs from the reference teachings only by the recitation of SEQ ID NO:1 in the claims.

However, the '430 teaches biologically active TGF-beta fragments consisting of amino acid sequences depicted in the sequence listing under SEQ ID NO:4 or SEQ ID NO:10. These biologically active TGF-beta fragments comprise of SEQ ID NO: 1 of the claimed invention. The biologically active TGF-beta fragments comprising of SEQ ID NO:4 or 10 are very potent biological agents which can be used therapeutically for different purposes. The fragments consisting of SEQ ID NOs:4 or 10 play a central role in many biological pathways including cell differentiation and wound healing (see col 2, lines 4-19, col 4, lines 29-59, col 4, lines 16-31, and sequence listing in particular).

It would have been obvious to one of the ordinary skill in the art at the time the invention was made to employ the biologically active TGF-beta fragments (i.e. SEQ ID NOs: 4 or 10) taught by the '430 patent in the immunogenic composition taught by the '085 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the TGF-beta fragments (i.e. SEQ ID NOs :4 or 10) taught by '430 patent are biologically active and therapeutically useful. As TGF-beta fragments would have the same immunostimulating effect as intact TGF-beta taught by '085 patent, it is expected that the TGF-fragments (i.e. SEQ ID NOs: 4 or 10) taught by the '430 patent would elicit the same immunostimulating effect in the immunogenic composition.

From the teachings of references, it would have been obvious to one of ordinary skill in art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of the ordinary in the art at the time of invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

17. No claims are allowable.

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yunsoo Kim whose telephone number is 571-272-3176. The examiner can normally be reached on Monday thru Friday 8:30 - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Yunsoo Kim
Patent Examiner
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December 8, 2004

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